first paragraph. The rejection is premised on the supposition that our Specification describes only leucine for the recited L_1-L_3. In fact, our Specification clearly describes L_1-L_3 as independently selected from hydrophobic amino acids, preferably leucine or isoleucine, more preferably leucine – exactly as recited in our claims. See Specification, p.4, lines 27-30. Furthermore, the same exact limitation on L_1-L_3 was present in original claim 6. Our written description is not limited to a particularly preferred embodiment.

35USC112, first paragraph - enablement

Claims 32-61 comply with the enablement requirement of 35USC112, first paragraph. The enablement issue is whether our Specification enables one of ordinary skill in the art to practice the invention without undue experimentation.

The first stated rejection, applied to claims 54-55, is premised on the suppositions that the claims encompass a sensor peptide comprising SEQ ID NO:11, that such a peptide does not work, and that the claims therefore require undue experimentation to practice. In fact, the claimed sensors (and respective methods) require a peptide that "works" – i.e. which provides direct, in vitro ligand-dependent binding to a nuclear hormone receptor. Hence, the claims do not encompass the supposed inoperable embodiments. Second, the Specification does not teach that use of a peptide comprising SEQ ID NO:11 is inoperable: the cited *exemplary* binding data of our Table 2 is limited to particular nuclear hormone receptors in a particular fluorescent polarization assay. Every combinatorially possible peptide will not and need not work with every receptor under every condition – in fact, assay specificity would be compromised if that were the case. Third, the claims would be compliant with the enablement requirement even if there were inoperable embodiments.[1] And fourth, ascertaining the suitability of any given candidate peptide species is well within the bounds of empirical experimentation permitted by the enablement

[1] "It is not a function of the claims to specifically exclude possible inoperative substances", *In re Dinh-Nguyen*, 181USPQ46,48(CCPA 1974); see also, *In re Wands* (8 USPQ2d 1400 (Fed Cir 1988), "Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation"; see also, *Atlas Powder Co.*, 224USPQ409,414 (Fed Cir 1994); and, as noted above, the claims do not even encompass such conceptual inoperative embodiments.

requirement of 35USC112, as defined by applicable Federal Circuit law; see *In re Wands* (8 USPQ2d 1400 (Fed Cir 1988). [2]

The second stated rejection, applied to claims 32-53 and 56-61, is premised on the same erroneous supposition as that of the written description rejection: that our Specification describes only leucine for the recited L_1-L_3. In fact, our Specification clearly teaches that L_1-L_3 are independently selected from hydrophobic amino acids, preferably leucine or isoleucine, more preferably leucine – exactly as recited in our claims. See Specification, p.4, lines 27-30. As noted above, the claimed sensors (and respective methods) require a peptide which provides direct, in vitro ligand-dependent binding to a nuclear hormone receptor. The Specification exemplifies the sensors and methods with a wide variety of suitable exemplary peptides with several receptors. Specification, p.5, line 24 - p.7, line 9. For additional sensor peptides, the Specification teaches that panels of predetermined or randomized candidate sensors are readily screened for differential binding, as exemplified in Figures 2 and 3 for two exemplary receptor/ligand pairs. Specification, p.5, lines 14-16. The assay is a rapid, high-throughput, simple in vitro binding assay, well within the bounds of empirical experimenation permitted by the enablement requirement of 35USC112 as defined by applicable Federal Circuit law, see e.g. *In re Wands* (supra).

The empirical experimentation necessary to practice alternative embodiments of our

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[2] In *Wands*, the Federal Circuit held that making and screening monoclonal antibodies, even back in 1980, did not constitute undue experimentation. Consider what is *not* undue experimentation: first, immunize, bleed and immunoassay panels of mice, wherein the immunoassay itself is a binding affinity assay; then, after immunizing and confirming the presence of requisite specific antibodies, practitioners of Wand's invention are faced with the daunting and unpredictable tasks of surgically removing the animal's spleen; separating lymphocytes therefrom; mixing the lymphocytes with myeloma cells; treating the mixture to cause a few of the lymphocytes to fuse with a few myeloma cells; isolating from the enormous number of cells in the mixture hybridoma cells that secrete the desired antibody through a series of screening procedures. The entire post-immunization process through serial cloning takes months. The technical feats involved include aseptic surgery, cell fusions, tissue culture with transformed cells which require special health and environmental safety measures, dilution cloning, usually into a bed of immature thymocytes which again requires further aseptic surgery, radiolabel or enzyme-linked immunoassays of secreted antibody, etc. In fact, the vast majority (>97%) of Wand's efforts to produce the claimed antibodies failed.

invention is trivial compared with that permitted under *Wands*. Substituting and testing an alternative hydrophobic amino acid for leucine in the finely taught, simple binding assays does not approach the experimentation required by Wands. Our Specification provides more than sufficient teaching to enable one of ordinary skill in this art to practice the claimed invention without undue experimentation. As the 35USC112-compliant experimentation required to generate and screen monoclonal antibodies per *Wands* is vastly more extensive and unpredictable than that required here, our claims are in compliance with the enablement requirement of 35USC112.

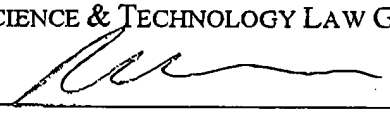
35USC112, second paragraph

The definiteness rejection is obviated by the foregoing formality amendments.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

Applicants hereby petition for a one month (small entity) and any necessary extension of time pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any fees or credit any overcharges relating to this communication to our Deposit Account No. 19-0750 (order no. T97-012-1).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



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VERSION SHOWING AMENDMENTS TO CLAIMS

32. (Amended) An in vitro assay method for modulators of a nuclear hormone receptor binding function, comprising steps:

forming an in vitro mixture comprising a first nuclear hormone receptor, a peptide sensor and a candidate agent, but not a natural coactivator protein of the first receptor, wherein the sensor consists of a peptide comprising the sequence $L_1X_1X_2L_2L_3$ (SEQ ID NO:18) covalently coupled to a detectable label, wherein L_1-L_3 are independently selected from hydrophobic amino acids and X_1-X_2 are independently selected from any amino acid and wherein the peptide provides direct, in vitro ligand-dependent binding to the first receptor and is 24 or fewer residues in length;

measuring an agent-biased binding of the sensor to the first receptor by detecting [the sensor of] immobilized first receptor-sensor complexes;

comparing the agent-biased binding with a corresponding unbiased binding of the sensor to the first receptor;

wherein a difference between the biased and unbiased bindings indicates that the agent modulates a binding function of the first receptor.

35. (Amended) A method according to claim 32, [wherein the sensor comprises a label and] wherein the measuring step, the first receptor is immobilized through the sensor and the sensor is immobilized through the label.

36. (Amended) A method according to claim 32, [wherein the sensor comprises a label and] wherein the measuring step, the first receptor is immobilized through the sensor, and the sensor is immobilized through the label by a second receptor.

37. (Amended) A method according to claim 32, [wherein the sensor comprises a label and] wherein the measuring step, the first receptor is immobilized through the sensor, and the sensor is immobilized through the label by a second receptor and wherein the measuring step comprises detecting the immobilized first receptor.

38. (Amended) A method according to claim 32, [wherein the sensor comprises a label and] wherein the measuring step, the first receptor is immobilized through the sensor, and the sensor is immobilized through the label by a second receptor and wherein the measuring step comprises detecting the immobilized first receptor with a third receptor.